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Comparison of the Effectiveness of Topical and Oral Beta Blockers in the Treatment of Childhood Hemangiomas

Çocukluk Çağı Hemanjiomlarının Tedavisinde Topikal ve Oral Beta-blokerlerin Etkinliğinin Karşılaştırılması

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Amaç: Hemanjiomlar çocukluk çağında en sık görülen vasküler tümörlerdir ve tedavi yaklaşımları son yıllarda köklü değişikliklere uğramıştır. Bu çalışma ile pediatrik yaş grubunda, beta blokerlerin topikal ve oral olmak üzere hemanjiyomlar üzerine etkinliği ve güvenilirliğini nonfarmakolojik tedavi ile karşılaştırmayı amaçladık.
Araçlar ve Yöntem: Hemanjiomlu çocuk hastalara ait tıbbi kayıtlar retrospektif olarak incelendi.
Bulgular: Çalışmaya elli üç hasta (K/E=40/13) dahil edildi. Hastaların 14'ünde (%26.4) yüzeyel hemanjiom, 39'unda (%73.6) derin hemanjiom saptandı. On yedi hasta ilaçsız izlendi, 19 hasta topikal beta bloker ve 17 hasta oral beta bloker ile tedavi edildi. Yüzeyel hemanjiomlu 12 hasta ilaçsız izlendi, 2 hasta topikal timolol tedavisi gördü.
Yüzeysel hemanjiyomlarda ilaçsız izleme göre topikal timololün iyileşme puanlarının daha yüksek olduğu ve ortalama solma ve lezyon derinliğinde azalmanın daha belirgin olduğu saptandı. (7.0'a karşı 1.66; p= 0.049; 6.0'a karşı 1.5; p=0.045).
Derin hemanjiyomlu hastalar oral ve topikal tedavi açısından karşılaştırıldığında, ortalama solma skorlarının hem 1. hem de 4. ayda grupları arasında fark göstermediği görüldü (p=0.551, p=0.551).
Sonuç: Gelecekte topikal tedavi yerine oral beta blokerlerin kullanılabileceği ve klinisyenler ve aileler tarafından daha az yan etkisi nedeniyle daha fazla tercih edileceğine inanıyoruz.

Anahtar Kelimeler: beta bloker; derin; hemanjiom; topikal; yüzeyel

ABSTRACT

Purpose: Hemangiomas are the most common vascular tumors in childhood, and the treatment options have undergone profound changes in recent years. In this study, we aimed to compare the efficacy and safety of beta-blockers on hemangiomas, both topical and oral, with non-pharmacological treatment in the pediatric age group.
Material and Methods: We retrospectively reviewed the medical records of pediatric patients with hemangiomas.
Results: Fifty-three patients (F/M=40/13) were enrolled in this study. Superficial hemangiomas were detected in 14 (26.4%) patients, and deep hemangiomas were detected in 39 (73.6%) patients. Seventeen patients were followed without medication, 19 were treated with a topical beta blocker, and 17 were treated with an oral beta blocker. Twelve patients with superficial hemangiomas were followed without medication, while two received topical timolol treatment. A comparison of lesion progression in patients with superficial hemangiomas in the non-pharmacological treatment and topical treatment groups showed that the mean scores of success, in terms of mean fading and reduction in lesion depth, were significantly higher at the first month (7.0 vs. 1.66; p=0.049; 6.0 vs. 1.5; p=0.045). Among patients with deep hemangiomas, a comparison of mean fading scores showed no difference between the oral and topical treatment groups in the first and fourth months (p=0.551, p=0.551).
Conclusion: We believe that oral beta-blockers can be used instead of topical treatment in the future, and they will be preferred more by clinicians and families due to less side effects.

Keywords: beta blocker; deep; hemangioma; superficial topical

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INTRODUCTION

Hemangiomas are common vascular tumors in pediatric age group. There are different treatment options of hemangiomas.[1,2] Oral corticosteroids have been used for many years in treatment and have provided favorable results. However, many side effects of oral corticosteroids have been observed, especially in their long-term and high-dose use, which has prompted the medical community to find new treatment options. Léauté-Labrèze et al. showed the effectiveness of oral beta blockers on hemangiomas.[3] Moreover, topical treatments have begun to be applied to minimize the potential side effects of the systemic use of beta blockers. Subsequently, studies have demonstrated the effectiveness of topical beta-blockers, particularly for superficial hemangiomas; several studies have reported that they are as effective as oral beta-blockers with fewer side effects.[4,6] On the other hand, only a few studies have investigated the effect of topical beta-blockers on deep hemangiomas, so their effectiveness in this indication has not been clarified. Therefore, we aimed to compare the effectiveness and safety of nonpharmacological treatment, topical beta-blocker treatment, and oral beta-blocker treatment in treating superficial and deep hemangiomas in the pediatric age group.

MATERIALS and METHODS

We retrospectively reviewed the medical records of hemangioma patients diagnosed in our center between January 1st, 2015, and June 1st, 2019. The ethics committee approval of the study was obtained from the Kirikkale University Clinical Research Ethics Committee (Date: 18.12.2019, Number: 2019.12.01).

The patients were divided into three groups according to the treatment strategy, i.e., nonpharmacological follow-up, topical timolol, and oral propranolol treatment. The size is recorded in mm^2 by multiplying the longest diameter of the hemangioma by the diameter and then intersecting this diameter by 90^o. A superficial USG was performed in all cases at admission. Cases were divided into two groups, superficial and deep hemangiomas, according to the depth of the hemangiomas in the dermis. Criteria for these patients to use only monitoring, topical timolol, and oral propranolol are shown in table 1.[7]

Table 1. Distribution of demographic and clinical characteristics of cases according to treatment groups.

Variables*	Drug free N=17	Topical N=19	Oral N=17
Gender (female) n (%)	12 (70.5)	14 (73.6)	14(82.3)
Gestational week (preterm)	1	4	3
Localization			
Head-Neck	5(29.4)	3(15.7)	6(35.3)
Trunk	5(29.4)	10(52.6)	5(29.4)
Extremity	6(35.3)	5(26.3)	2(11.7)
Anogenital	0 (0)	0(0)	3(17.6)
Multiple	1(5.9)	1(5.3)	1(5.9)
Depth (Deep)	5(29.4)	17(89.5)	17(100)

Oral propranolol tablets are given at a dose of 1 mg/kg/day, as a topical beta-blocker in the form of timolol maleate 0.5% eye drops is preferred. Lesions larger than 1 cm received one drop of timolol per bid, lesions between 1 and 2 cm received two drops per bid, and lesions greater than 2 cm received three drops per bid. The effectiveness of these treatment strategies was compared in terms of efficiency and safety. In evaluating the efficiency, the fading of the lesion's color, the reduction of the swelling, and the reduction of its mean area were considered, and the improvement scores were calculated. Clinicians were asked to evaluate the fading of the hemangioma and reduction of swelling as "present" or "absent." A yes answer was recorded as a "1" point, and a no answer was recorded as a "0" point. For each case, the "yes" answers of 10 research assistants were recorded as the "recovery score" out of 10 points. Field measurements evaluated the reduction in the size of the hemangioma. The calculated reduction in the area in mm^2 was compared between the treatment groups.

Statistical Analysis

The study data were analyzed using IBM® SPSS (Statistical Package for the Social Sciences) version 20.0 software (SPSS Inc.). Categorical variables are expressed as frequencies(n) and percentages(%), and continuous variables are expressed as means and standard deviations. The statistical analyses were performed with the chi-square test, Mann-Whitney U test, Kruskal-Wallis test, Friedman test, and Wilcoxon test. $p<0.05$ was considered statistically significant.

RESULTS

Fifty-three pediatric patients (F/M=13/40) were enrolled in this study. The distribution of the patients into study groups according to their demographic and clinical characteristics is given in Table 2.

Table 2. Distribution of demographic and clinical characteristics of cases according to treatment groups.

Variables*	Drug free N=17	Topical N=19	Oral N=17
Gender (female) n (%)	12 (70.5)	14 (73.6)	14 (82.3)
Gestational week (preterm)	1	4	3
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Head-Neck	5 (29.4)	3 (15.7)	6 (35.3)
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Extremity	6 (35.3)	5 (26.3)	2 (11.7)
Anogenital	0 (0)	0 (0)	3 (17.6)
Multiple	1 (5.9)	1 (5.3)	1 (5.9)
Depth (Deep)	5 (29.4)	17 (89.5)	17 (100)

Superficial hemangiomas were detected in fourteen (26.4%) patients, and deep hemangiomas were detected in thirty-nine (73.6%) patients. Seventeen (32.1%) patients were followed without medication, i.e., the "drug-free group." nineteen (35.8%) patients were treated with a topical beta-blocker (Timolol), and seventeen (32.1%) patients were treated with an oral beta-blocker (Propranolol). The mean age of the study population was 10.8 months. Forty-five (84.9%) patients were born at term, and eight (15.1%) had a history of preterm birth. The gender distribution of the groups is shown in Table 2. There was a female predominance in all groups. According to the location of the hemangioma, fourteen (26.4%) patients had a lesion in the head or neck, twenty (30.7%) patients in the trunk, thirteen (24.5%) patients in the upper or lower extremities, three (5.7%) patients in the anogenital region, and three (5.7%) patients in multiple regions. Ulceration was the only complication detected in three (5.7%) patients. All patients with ulceration were taking oral propranolol.

Twelve of the 14 patients with a superficial hemangioma were followed without medication, while two received topical timolol treatment. A comparison of the lesion progress in the patients with superficial hemangiomas in the nonpharmacological treatment and topical treatment groups showed that the mean scores of success in terms of mean fading and reduction in lesion depth were significantly higher during the first month (7.0 (range5-9) vs. 1.66 (range 0-6); p=0.049; 6.0 (range 4-8) vs. 1.5 (0-6); p=0.045). However, the fourth month was the same (Table 3).

Table 3. Comparisons of drug-free follow-up and topical treatment groups in superficial hemangiomas.

Variables*	Drug free N=12 Mean score (range)	Topical N=2 Mean score (range)	P value
Fading after 1 month	1.66 (0-6)	7.0(5-9)	0.049
Fading after 4 month	2.16(0-7)	7.5(5-10)	0.065
Decrease in depth after 1 month	1.50(0-6)	6.0(4-8)	0.045
Decrease in depth after 4 month	1.83(0-6)	7.0(5-9)	0.062

Among patients with deep hemangiomas, a comparison of mean fading scores showed no difference between the oral and topical treatment groups in the first and fourth months (p=0.551, p=0.551). There was no difference in the mean reduction in lesion depth in the first and fourth months between the topical and oral treatments (p=0.999, p= 0.999). On the other hand, the mean size reduction and fading scores of both the topical and oral treatment groups were significantly higher than those of the nonpharmacological follow-up group (Table 4).

Table 4. Comparisons of scores between the drug-free follow-up, topical, and oral treatment groups in deep hemangiomas.

	Mean score			Mean score			Mean score		
	Drug free	Topical	p	Drug free	Oral	p	Topical	Oral	p
Fading after 1 month	2.00	7.64	0.001[a]	2.00	7.76	0.019[a]	7.64	7.76	0.551[a]
Fading after 4 month	2.40	8.41	0.001[a]	2.40	8.58	0.019[a]	8.41	8.58	0.551[a]
Decrease in depth after 1 month	1.80	7.00	0.010[a]	1.80	6.94	0.039[a]	7.00	6.94	1.000[a]
Decrease in depth after 4 month	1.80	7.47	0.019[a]	1.80	7.82	0.019[a]	7.47	7.82	1.000[a]

In Figure 1, two patient responses to the topical treatment are shown. No reduction in hemangioma size was observed during the follow-up period in the drug-free group in superficial hemangiomas.

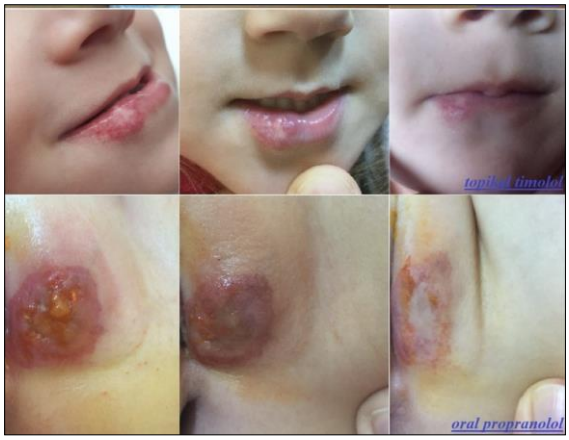

Figure 1. Photographs of two of our patients with deep hemangiomas at the time of admission and at the first and fourth months after topical and oral propranolol treatment.

The mean hemangioma size in the topical timolol group was 237.50 mm^2 at admission, 187.50 mm^2 during the first month, and 150.00 mm^2 in the fourth month. In superficial hemangiomas, no significant difference was observed during the follow-up period in the topical timolol group after the first and fourth months (p=0.365 and 0.156, p=0.156) group. (Table 4). No reduction in hemangioma size was observed during the follow-up period in the nonpharmacological follow-up group in deep hemangiomas. The mean hemangioma size in the topical timolol group was 302.82 mm^2 at admission, 261.11 mm^2 during the first month, and 215.52 mm^2 in the fourth month. A significant reduction compared with the admission size was found in the topical timolol group in the first month (p=0.002) and fourth month (p=0.001). The mean hemangioma size in the oral propranolol group was 690.64 mm^2 at admission, 589.70 mm2 in the first month, and 490.29 mm2 in the fourth month. A statistically significant reduction compared with the admission size was found in the oral propranolol group in the first month (p=0.001) and fourth month (p=0.001) (Table 5, Figure 2).

Table 5. Comparison of the mean areas of hemangioma in the treatment groups in superficial and deep hemangiomas at admission. the first month. and the fourth month of follow-up.

		Beginning	**1. month**		**4.month**		
		Mean area	Mean area	p	Mean area		p
Superficial	Drug free	424.08	424.08	-	424.08	-	
	Topical	237.50	187.50	0.368-	150.00	-	0.156
Deep	Drug free	416.00	416.00	-	416.00	-	
	Topical	302.82	261.11	0.002	215.52		0.001
	Oral	690.64	589.70	0.001	490.29		0.001

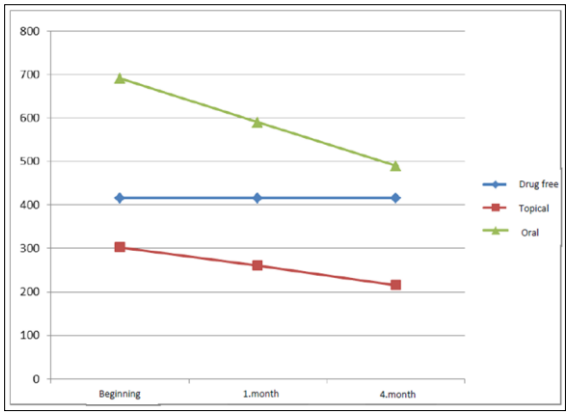

Figure 2. Comparison of the size reduction in deep hemangiomas between the drug-free. topical timolol. and oral propranolol groups during the follow-up.

Because propranolol could cause side effects, blood pressure, pulse rate, and blood glucose levels were measured in the first and fourth months, and patient complaints were recorded between control visits in all patients receiving propranolol treatment. No side effects were observed in patients treated with topical timolol. Insomnia and sleep disorders were reported by the parents of 2 patients treated with oral propranolol. Blood pressure, pulse rate, and blood glucose measurements were performed in all patients receiving drug treatment; hypotension, bradycardia, and hypoglycemia were not observed in any group. No dose restriction was made for patients taking oral or topical beta-blockers, and it was learned from the records of the control visits that side effects did not recur.

DISCUSSION

The treatment options for hemangiomas in children have undergone radical changes in recent years. Oral propranolol and topical beta-blockers are the recently approved options in the treatment of hemangiomas. To avoid the side

effects that may occur with oral beta-blockers in infants, topical treatment has begun to be favored. Our study compared the effectiveness and safety of oral and topical beta-blocker treatments used in treating hemangiomas in our clinic.

It has been reported in the literature that hemangiomas are more common in girls and premature babies. It was reported that hemangiomas are 3.07 times more common in girls than boys.[5,8] We found similar data in our study. We found a hemangioma prevalence of 15.1% among our prematurely born patients. Similarly, Amir J. et al. found a prevalence of 12.7%, and Wu et al. found a prevalence of 20.85%.[5,9]

Although infantile hemangiomas can be seen in every body part, they are most commonly located in the neck region.[5,10] In our study, the trunk was the most commonly involved body region (37.7%). Such a high prevalence of trunk hemangiomas was likely caused by excluding the more common head-neck hemangiomas. Similarly, Xu et al.[11] found a high prevalence of trunk involvement (51.28%). Unlike previous studies,[12,13] our study found that deep hemangiomas predominated (73.6%). The anxiety caused by the appearance of deep hemangiomas in families may have contributed to the high presentation rate of patients with deep hemangiomas. The complications of deep hemangiomas are also a reason for referral and increase parental anxiety and awareness. Ulceration occurred in three patients who had propranolol treatment. In a 6-month study, Chan et al. compared a low dose (0.5 mg/day) of topical timolol to a placebo in superficial hemangiomas and found that the topical therapy was more effective than the placebo.[14] Wu et al., [5] on the other hand, showed that topical timolol 0.5% was effective at higher doses. The higher response rate in our study compared with those studies may be because we used higher timolol doses. The superiority of the effectiveness of topical timolol over a nonpharmacological follow-up could not be shown due to the insufficient number of patients with superficial hemangiomas who received topical treatment. In patients treated with topical timolol, paleness of the hemangioma was observed in a short time.

Since the first use of oral propranolol in treating hemangiomas in 2008, its effectiveness and safety have been confirmed in previous studies.[15,16] Kaneko T et al.[17] examined the effectiveness of oral propranolol used at a dose of 3 mg/kg/day in cases of infantile hemangioma in Japan and reported a complete recovery rate of 80% after a 24-week follow-up. In a study conducted by Sans et al.[18] in France, oral propranolol was given to 32 patients at a dose of 2-3 mg/kg/day for six months, and almost complete recovery was observed in all cases. The first reported study in our country in 2010, conducted by Erbay et al.,[19] also showed its effectiveness and safety. In our study, although oral propranolol was used at a lower dose and for a shorter period in patients with deep hemangiomas than those reported in the literature, the effectiveness of treatment was higher than that of a nonpharmacological follow-up and topical timolol treatment. Although there was no significant difference in pallor, the magnitude of depth reduction was significant between the oral propranolol group and the topical treatment and nonpharmacological follow-up groups. With oral propranolol treatment for deep hemangiomas, the average growth size went from 690 mm^2 when the patient was admitted to 589 mm^2 after one month and 490 mm^2 after four months. At the end of the total follow-up, most patients fully recovered.

As in all treatment choices, side effects should be considered when treating hemangiomas, and the drug with the fewest side effects should be preferred. In a study by Wu et al.,[5] topical timolol resulted in no systemic side effects, but mild local side effects such as local itching and skin spots in 12 patients were observed. In that study, sleep disturbance, diarrhea, loss of appetite, acromegaly, and bronchial spasm were found in 14 patients after oral propranolol. Local side effects were more common with topical timolol than oral propranolol, but systemic side effects were more common with oral propranolol.[5] It is known that side effects such as hypotension, bradycardia, hypoglycemia, and arrhythmia may occur after oral propranolol use.[20] In a study conducted in Japan, at least one side effect was observed in 31 of the 32 cases treated with oral propranolol at a dose of 3 mg/kg/day.[17] While no systemic side effects were reported after the use of topical timolol, it was emphasized that there might be local effects.[14]

Our study has several limitations. First, it had a small sample size, especially for patients with superficial hemangiomas treated topically. Second, this study was conducted in a single center, so its results regarding the prevalence of these lesions cannot be generalized to the total population.

Conclusion

Topical treatment can replace oral beta blockers in the future and will likely be preferred by clinicians and families because of its fewer side effects. We want to stress that the treatment of infantile hemangiomas should be based on the patient's age, the size of the hemangioma, any complications, a delicate balance between the benefits of treatment and the side effects, and the level of anxiety in the parents.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

The study was approved by Kırıkkale University Non-Invasive Studies Ethics Committee (18.12.2019-2019/20).

Authors' Contributions

Concept/Design: KFY, MA, YK. Data Collection and/or Processing: KFY, AA, SNV, ST. Data analysis and interpretation: KFY, MA, ST. Literature Search: YK, AA, SNV. Drafting manuscript: KFY, YK, ST, AA. Critical revision of manuscript: MA, KF, AA. Supervisor: YK, AA, MA.

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